REMARKS

Reconsideration is respectfully requested.

The Examiner asserted in the communication of August 1, 2005 that the response of May 23, 2005 was not responsive. Specifically, the Examiner asserts that the claim amendments are the subject of a different invention than originally claimed. Applicants response is therefore directed to the original claim set amended as of March 11, 2004.

Claims 1-26 have been cancelled. Claims 27-36 have been added. New claims 27-36 correspond to claims 1-17. In particular, claim 27 corresponds to claims 1 incorporating the limitations of claims 5 and 16.

Applicants have included specific steps of Protein Design Automation as described in the specification to specify steps of the claimed invention, including the working examples. Accordingly, the amendments do not present new matter and entry is proper.

Claim Rejections under 35 U.S.C. § 112, second paragraph

The Examiner rejected claims 13 and 14 as directed to a secondary sequence.

Applicants have cancelled claim 13. Claim 36 corresponds to now cancelled claim 14, and new claim 27, and has been amended to depend from claim 1. This ground for rejection is moot. Applicants respectfully request that it be withdrawn.

Claim Rejections under 35 U.S.C. § 112, first paragraph

The Examiner rejects Claims 1, 2, 5-7, 10-14, 16 and 17 under 35 U.S.C. 112, first paragraph as not being enabled by the specification. Applicants respectfully traverse.

A. Legal Standard

Under 35 U.S.C. §112 ¶ 1, a patent specification containing a teaching of how to make and use the invention must be taken as enabling unless the PTO provides sufficient reason to doubt the accuracy of the disclosure. *In re Marzocchi*, 439 F.2d 220, 223-224, 169 U.S.P.Q. 367, 369-370 (C.C.P.A. 1971).

The claimed invention as disclosed in the specification cannot be questioned on the unsupported skepticism of the Examiner. *Ex parte Linn*, 123 U.S.P.Q. 262 (PTO Bd. Pt. App. Int. 1959); *Ex parte Rosenwald*, 123 U.S.P.Q. 261 (PTO Bd. Pt. App. Int. 1959) (emphasis added). The number and variety of examples is irrelevant in the disclosure is

"enabling" and set forth the "best mode contemplated." Even in an unpredictable art, Section 112 does not require disclosure of a test of every species encompassed by the claims. *In re Angstadt*, 190 U.S.P.Q. 214, 218 (C.C.P.A. 1976).

An invention is enabled even though the disclosure may require some routine experimentation to practice the invention. *Hybritech v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1384, 231 U.S.P.Q. 81, 94 (Fed. Cir. 1986). The fact that the required experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation. *ML T v. A.B. Fortia*, 774 F.2d 1104, 227 U.S.P.Q. 428 (Fed. Cir. 1985). A considerable amount of experimentation is permitted if it is merely routine or the specification provides a reasonable amount of guidance and direction to the experimentation. *In re Wands*, 858 F.2d 731, 8 U.S.P.Q.2d 1400 (Fed. Cir. 1988); In re *Jackson*, 217 U.S.P.Q. 804, 807 (PTO Pt. Bd. App. Int. 1982) (emphasis added). Finally, the Examiner has the burden of showing that the disclosure entails undue experimentation. *In re Angstadt*, 537 F.2d 498, 190 U.S.P.Q. 214 (CCPA 1976) (emphasis added).

B. Meeting the Legal Standard

The Examiner's grounds for lack of enablement are focused on assertions that the scope of disclosure and working examples supporting the step of "inserting an active site domain," the strategy for insuring that the claimed method would retain enzymatic activity, and the state of the art at the time of the presently claimed invention all militate against enablement.

Because the Examiner's characterization of the specification and examples are incorrect, Applicants respectfully disagree.

Inserting an active site domain

Examiner argues that Example 1 at pages 50-55 does not demonstrate insertion of "an active site domain" as required by the claimed method.

Contrary to the Examiner's position, the working example teaches insertion of a catalytic histidine into a thioredoxin scaffold. The catalytic histidine is the "active site domain." At page 50, the example discloses that "candidate variant protein sequences with catalytic histidine at different positions in thioredoxin were ranked based on recognition of the high energy state rotamer." The example further describes calculation

methodology, including generating a library of high-energy rotamers and application of the forcefield to high-energy rotamers.

The working example is consistent with the description provided by the specification. As described above, the specification describes "active site domains" beginning at page 9, line 28, and provides a description of "active site domain" as a "ligand binding domain" (Specification page 11 lines 9-17). Candidate proteins with putative enzyme-like activity are then generated. Alternatively, an active site domain can be chosen, followed by choosing an appropriate scaffold. (Specification, page 12 lines 10-14).

As such, both the working examples and specification provide an extensive discussion of inserting a catalytic domain into a structural protein. The Examiner's position that the claimed invention lacks enablement on this ground is misplaced.

Retention of enzymatic activity

The Examiner states that there is no "guidance in the specification on how to insert an 'active' domain into the scaffold, and how to combine said insertion of the active domain with protein design so that at the end the variant protein maintains enzyme-like activity."

Applicants again respectfully disagree. Contrary to the Examiner's position, the presently claimed invention is directed to expressing and testing the activity of a designed protein is the optimal coherent strategy to ensure the claimed protein design method yields a protein with enzyme-like activity. The specification provides specific guidance as to how to combine the insertion of the active domain with protein design automation to maintain enzymatic activity. The specification discloses production of active sites in a protein scaffold. The specification further discloses an alternative methodology in which an active site domain can be chosen, followed by choosing an appropriate scaffold. (Specification, page 12 lines 10-14). Candidate proteins with putative enzyme-like activity are then generated, synthesized, and tested to select the candidate with enzyme-like activity.

The successful application of the teachings of the specification is demonstrated in the working example. After the protozyme is designed, it is synthesized and validated experimentally to test for activity. Synthesis of the protein are disclosed in the

Specification from page 52, line 28 through page 53, line 27. Two proteins (protozymes) were expressed and their activity and specificity measured. The tests confirmed that both proteins had both enzymatic activity and specificity. The demonstration of retention of activity further bolsters the support found in the specification.

The State of the Art

The Examiner cites a number of references in the art to support the conclusion that the state of the art is unpredictable. Specifically, the Examiner cites Brenner for the proposition that protein design is too complex to be accomplished, and Dejarlais (reference C21) for the proposition that "designing proteins with well designed structures and properties that mimic those of natural proteins remain elusive." (Desjarlais, Abstract).

The art cited by the Examiner is directed to general protein design, and is not focused on the presently claimed invention. Moreover, Applicants do not point to the art for a full disclosure of how to perform the claimed methods – only selected portions of the claimed method steps. The specification, in combination with the working example, provides extensive description of how to perform the claimed invention and overcome the limitations stated by the references cited by the Examiner.

None of the cited references critique the presently claimed method. Dejarlais does not teach the presently claimed method of using PDA in the context of combining a protein scaffold with an active site domain. Instead, the reference provides a general discussion of protein design methods. Brenner critiques to general methods of designing proteins, but does not critique the presently claimed method. In short, the presently claimed invention provides a solution to specific problems broadly identified in the art.

As such, the Examiner's position on lack of enablement is incorrect. Applicants have described how to make and use the presently claimed methods. This ground for rejection should be withdrawn.

Claim Rejections under 35 U.S.C. § 102 – WO 98/53849

In order to anticipate under § 102, every element of the claimed invention must be identically shown in a single reference. *In re Bond,* 910 F.2d 831, 15 USPQ2d 1566 (Fed. Cir. 1990).

WO 98/53849 does not teach or disclose an "insertion step [comprising] the use of at least one high energy state rotamer," or a "automation algorithm using high energy rotamers comprising" a series of steps specific to protein design automation. Instead, WO 98/53849 discloses a generic protein substitution method in which a metal center is introduced by the DEZYMER protein algorithm. The DEZYMER algorithm does not include the claimed method steps. As such, the claims are not anticipated by WO 98/53849.

Applicants respectfully request that this ground for rejection be withdrawn.

Rejections under 35 U.S.C. § 102 – Robertson, Hellinga, and Klemba

Claims 1, 2, 5-7, 14, 15, and 16 stand rejected alternatively over Robertson, Hellinga, and Klemba.

The presently claimed invention is not anticipated by any of the cited references. Specifically, none of the cited references teach or disclose an "insertion step [comprising] the use of at least one high energy state rotamer," or a "protein design automation algorithm using high energy rotamers comprising" the claimed steps.

Robertson teaches design of four-helix dimers with two-fold symmetry and four parallel haem groups. Robertson does not disclose insertion using at least one high energy state rotamer, nor step of protein design automation. As such, Robertson fails to anticipate the presently claimed method.

Hellinger, like WO 98/53849, discloses introducing new ligand binding sites using the DEZYMER molecular modeling computer algorithm. As stated in the Hellinger Abstract, the DEZYMER program introduces binding sites "by taking into account simple rules such as steric hinderance, atomic close-packing and hydrogen bond patterns." Hellinger neither discloses nor claims an "insertion step [comprising] the use of at least one high energy state rotamer," or a "protein design automation algorithm using high energy rotamers comprising" steps specific to PDA. As such, Hellinger differs fundamentally from the presently claimed methods.

Likewise, Klemba does not anticipate the claimed invention. Klemba teaches designing novel metal binding sites, but does not teach insertion using at least one high

energy state rotamer, or a step of protein design automation as claimed. As such, Klemba fails to anticipate the presently claimed method.

Applicants respectfully request that this ground for rejection be withdrawn.

Rejections under 35 U.S.C. § 103(a) – WO 98/53849 in view of Robertson Hellinga, and Klemba

Claims 10-12, 16, and 17 stand rejected over WO 98/53849 in view of Robertson, Hellinga, and Klemba.

1. The cited references fail to anticipate the presently claimed methods.

To render a claim obvious, the references, in combination, must teach every element of the rejected claims.

As discussed above, none of the references teach the presently claimed invention. WO 98/53849 and Hellinga does not teach or disclose an "insertion step [comprising] the use of at least one high energy state rotamer," or a "protein design automation algorithm using high energy rotamers comprising" the specific steps. Instead, the references teach a generic protein substitution method in which a metal center is introduced by the DEZYMER protein algorithm. While both references are directed to refining a protein structure to include a metal center, the way in which the metal center is inserted does not include the steps if of the presently claimed method. As such, neither WO 98/53849 nor Hellinga discloses the presently claimed invention.

Robertson does not provide the requisite teachings absent in WO 98/53849 and Hellinga. Robertson teaches design of four-helix dimers with two-fold symmetry and four parallel haem groups. Robertson does not disclose insertion using at least one high energy state rotamer, nor step of protein design automation.

Similarly, Klemba does not provide the requisite teachings absent in WO 98/53849 and Hellinga. As discussed above, Klemba teaches designing novel metal binding sites, but does not teach insertion using at least one high energy state rotamer, or a step of protein design automation as claimed.

Brenner also fails to provide the requisite missing method steps.

Examiner's Argument

The Examiner further states that "if there are any differences between Applicant's claimed methods and that of the prior art, the difference would appear to be minor in nature." The Examiner asserts that "it would be conventional and within the skill of the art to select appropriate protein design steps because the techniques of computational protein design are known in the art ...and because the selection of appropriate protein design steps is conventional and within the skill in the art."

Assertions of "minor differences" without citation to specific references are insufficient to satisfy the requirements for obviousness. As disclosed above, the claims are not taught by the cited references. The presently claimed invention is therefore not taught by the cited reference, and the claimed methods are clearly not conventional because they are not disclosed by, and therefore not obvious over, anticipated by the cited references.

2. The cited references fail to provide the requisite motivation or suggestion to combine their teachings and make the claimed invention.

The cited references in combination fail to provide the requisite motivation or suggestion to alter their teaching and make the presently claimed invention. As discussed in detail above, the references in combination fail to teach every element of the claimed methods. As such, there is no teaching in any of the references that would point one of ordinary skill in the art to amend the teachings of the reference to perform the presently claimed methods. Therefore, the references in combination fail to provide the requisite motivation or suggestion to alter the teachings of the cited references.

3. The cited references in combination fail to provide a reasonable expectation of success

The cited references in combination fail to provide a reasonable expectation of success for altering their teachings to make the presently claimed invention. There is no teaching in any of the references that would point one of ordinary skill in the art to amend the teachings of the reference to perform the presently claimed methods – particularly since the missing method steps are not present in the cited references. Therefore, the references in combination fail to provide the requisite reasonable expectation of success in performing the claimed methods.

Applicants respectfully request that this ground for rejection be withdrawn.

Rejections under 35 U.S.C. § 103 – USSN 6,188,965 to Mayo in view of various references

Claims 1, 2, 5-7, 13, 14, and 16 stand rejected over 35 U.S.C. § 103 as obvious over "references teaching protein design methods (e.g. US Patents 6,188,965, US 6,269,312, and other references cited on lines 35 to p.3, line 2) in view of Anderson et al. (US 6180343).

USSN 6,188,965 and USSN 6,269,312 are clear, but there are no references cited at "lines 35 to p.3, line 2," as stated by the Examiner. Absent a clear identification of the cited art, Applicants cannot effectively respond to the Office Action. Accordingly, Applicants response is directed to USSN 6,188,965 (the '965 patent) and USSN 6,269,312 (the '312 patent) both of which are assigned to the California Institute of Technology.

Under 35 U.S.C. § 103(c)(1), neither the '965 patent nor the '312 patent can preclude patentability of the presently claimed invention under U.S.C. § 103.

35 U.S.C. § 103(c)(1) states:

> [s]ubject matter developed by another person, which qualifies as prior art only under one or more of subsections (e), (f), and (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the claimed invention was made, owned by the same person or subject to an obligation of assignment to the same person.

Neither the '965 patent nor the '312 patent can be used in an obvious rejection under 35 U.S.C. § 103(a) because the references 1) only qualify as prior art under 35 U.S.C. § 102(e), (f), or (g), and 2) were owned by the same entity or subject to an obligation of assignment to the same entity as the instant application at the time the claimed invention was made.

1. Both the '965 patent and the '312 patent only qualify as art under 35 U.S.C. § 102(e).

The instant application claims priority to U.S. Provisional Application No. 60/267,602, filed February 9, 2001.

The '965 patent issued February 13, 2001. Because issue date of the '965 patent is after the priority date of the instant application, the '965 patent was not a printed publication before the priority date (§ 102(a)) or a printed publication over a year before the priority date (§ 102(b)).

Likewise, the '312 patent issued July 31, 2001. Because issue date of the '312 patent is after the priority date of the instant application, the '312 patent was not a printed publication before the priority date (§ 102(a)) or a printed publication over a year before the priority date (§ 102(b)). Neither reference is a prior art reference under 35 U.S.C. §§ 102(c) or 102(d).

Therefore, the cited references could only be considered as prior art under 35 U.S.C. §§ 102(e), (f), or (g).

2. Statement of Common Ownership

In accordance with the requirements to establish common ownership articulated in M.P.E.P. § 706.02(l)(2), the instant U.S. Patent Application No. 10/074,679 and the '965 patent and the '312 patent were, at the time the invention of the instant application was made, owned by The California Institute of Technology.

Therefore, according to U.S.C. § 103(c)(1), the '965 patent and the '312 patent cannot preclude patentability of the presently claimed invention under U.S.C. § 103. Because this ground for rejection is improper, Applicants respectfully request that it be withdrawn.

Conclusion

Please direct further questions in connection with this Application to the undersigned at (415) 781-1989.

Respectfully submitted,

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